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Investigation of peripheral natural killer cell activity in recurrent miscarriages of unknown cause

Peripheral natural killer cell activity ın recurrent miscarriages of unknown cause

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Abstract
Aim: Recent studies on alloimmune factors have shown that Natural Killer (NK) cells may have a role in the implantation and maintenance of pregnancy. It is unclear precisely what kind of relationship exists between uterine and peripheral blood NK cells. Our study aims to investigate the relationship between pNK cells and recurrent pregnancy loss.
Material and Methods: Among the patients who applied to the outpatient clinic at University Hospital, retrospectively, women with two or more pregnancy losses constituted the RM group, and women with two or more live births and no miscarriage formed the control group. Two or more miscarriages before 20 weeks of gestation were accepted as the criterion to consider a case of recurrent pregnancy loss.
Results: To investigate the etiology of miscarriage in RM patients, parameters associated with the cytotoxicity of pNK cells in women with RM and control fertile women were evaluated. Although the median pNK activity level was relatively higher in the recurrent low group compared to the control group, there was no significant difference between the groups in our study (p=0.448).
Discussion: The present study found no significant difference in the percentages of CD56+dim and CD56+bright pNK cells between the patient group with unexplained RM and the healthy fertile control group. There was also no significant difference in CD8 and CD158a expressions in pNK cells between the patient group with unexplained RM and the healthy fertile control group.

Keywords
Peripheral Natural Killer Cell , Recurrent Miscarriages, Alloimmune Factors

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Introduction

Recurrent miscarriage (RM) or recurrent pregnancy loss (RPL) is an early pregnancy complication affecting approximately 1-3% of couples of reproductive age. American Society for Reproductive Medicine (ASRM) defines RM as two or more spontaneous pregnancy losses, not necessarily consecutive, before the 20th week of pregnancy [1]. the European Society for Human Reproduction and Embryology (ESHRE) defines it as three or more consecutive pregnancy losses (not necessarily intrauterine) [2]. RM's etiology includes coagulation system disorders, genetic disorders, anatomical factors, immunological causes, hormonal disorders, and environmental causes. Immunologic causes account for 20–50% of all recurrent pregnancy losses [3].

Recent studies on alloimmune factors have shown that Natural Killer (NK) cells may have a role in the implantation and maintenance of pregnancy. Since NK cells are the predominant leukocyte population in the endometrium during implantation and early pregnancy, the most extensive studies have been conducted on these cells. NK cells are divided into peripheral NK (pNK) and uterine NK (uNK) cells. Phenotypically, they are categorized into two types:

1-CD56 positive CD16 negative NK cells (referred to as CD56 bright)

2-CD56 positive CD16 positive NK cells (referred to as CD56 dim) [4].

In the peripheral blood, the main population of NK cells (90%) is CD56 dim cells. They are potent mediators of natural cytotoxicity and are more cytotoxic than other NK subsets. These cells are in direct contact with chorionic villi in the intermittent space, and the ability of the developing fetus to evade NK cytotoxicity from these cells may determine pregnancy outcome [6–8]. The cytotoxic CD56 dim subset has been reported to be up-regulated in the peripheral blood of women with RM compared to healthy fertile women [5-7]. Uterine NK (uNK) cells are predominantly CD56 bright CD16 cells. From a histological perspective, uNK cells are much more granulated than pNK and exhibit a greater immunomodulatory role than the pNK subset, which has potent cytolytic activity [8]. The origin of uterine NK cells is still unknown. Uterine NK cells are mainly CD56 bright CD16- cells with a more immunoregulatory role. Endometrial NK (eNK) cells represent one-third of total lymphocytes in the endometrium and may be involved in embryo implantation. Once pregnancy has occurred, decidual NK (dNK) cells become the predominant subset of lymphocytes in the uterus and contribute to the maintenance of the pregnancy [9].

NK cells can be classified as NK1 and NK2 based on their distinct cytokine production profiles. The NK1 type mainly produces IFN-γ and Tumor necrosis factor α (TNF-α), while the NK2 type primarily secretes IL-4, IL-5, IL-10, and IL-13. A shift from NK1 to NK2 profile has been documented to be necessary for healthy pregnancies [10]. Indeed, peripheral blood CD56 bright NK cells of women with a history of RM were found to have proportionally lower levels of IL-4 and IL-10 and higher levels of IFN-γ and TNF-α than healthy controls, indicating an increase in the NK1/NK2 ratio [11]. On the other hand, RM patients are thought to have a more active immune system balanced by the secretion of immunoregulatory cytokines compared to healthy women, while there is an increase in NK cells producing IFN-γ and immunosuppressive TGF-β and IL4 [7].

Some studies have shown that the CD8+ NK subset is more cytolytic than its CD8- NK counterpart. Besides, NK cells with higher CD8+ expression were suggested to be more active [12, 13]. However, other studies have shown that NK cytolytic activity is directly related to CD158 a/b in NK cells [14].

NK cell function in human reproduction is currently poorly understood. Studies have shown changes in the NK cell population in recurrent pregnancy loss and infertility. It is unclear precisely what kind of relationship exists between uterine and peripheral blood NK cells. Our study aims to investigate the relationship between pNK cells and recurrent pregnancy loss.

Material and Methods

Among the patients who applied to the outpatient clinic of Necmettin Erbakan University Meram Medical Faculty Hospital Gynecology and Obstetrics Clinic between January 2020 and January 2021, women with two or more pregnancy losses constituted the RM group and women with two or more live births and no miscarriage formed the control group. Two or more miscarriages before 20 weeks of gestation were accepted as a criterion to consider a case of recurrent pregnancy loss.

A total of 30 patients aged 20-40 years with recurrent pregnancy loss were included in the study. All women had a normal parental chromosome. All of them were negative for antiphospholipid antibodies (ANA, Anti DNA, Anticardiolipin-IgM, Anticardiolipin-IgG, Antiphospholipid-IgM, Antiphospholipid Ig-G), Anti Toxoplasma-IgM, Antirubella-IgM, hypothyroidism or hyperthyroidism (free T4 and TSH values were checked). All patients had a normal HSG, and none had cervical incompetence, which was checked with the No. 8 Hegar plug on day 26 of the menstrual cycle. None of the patients presented thrombophilia criteria (Antithrombin III deficiency, Protein C deficiency, Protein S deficiency, Factor V Leiden mutation, Prothrombin 2010 mutation, MTHFR 677 mutation, MTHFR 1298 mutation). Acar K, Management Of HIgh RIsk EssentIal Thrombocythemia In Pregnant WIth Recurrent Pregnancy Loss. Selcuk Medical Journal, 2009; 25. 3: 167-170. The control group consisted of 10 women between the ages of 20 and 40 who applied to the Necmettin Erbakan University Meram Medical Faculty Hospital Gynecology and Obstetrics Clinic and had two or more births and no history of pregnancy loss. Demographic and clinical characteristics of the participants were recorded at hospital admission. The patients included in the study were selected randomly according to the order of admission to the outpatient clinic. Those included in the control group were assigned by simple random sampling.

Blood samples of all RM and control groups were analyzed at the Microgen Genetic Diseases Diagnosis Center laboratory in Ankara. The ELISA method determined NK cell activity from peripheral blood samples with the NK VUE test kit. The reference range for the activated NK test was accepted as <1800 pg/ml.

Statistical analysis: For statistical analysis, all collected data were analyzed with the Statistical Package for the Social Sciences, version 20, SPSS Inc., Chicago, IL (SPSS). The Kolmogorov-Smirnov test and histograms determined the conformity of data to normal distribution. Normally distributed

continuous variables were analyzed with the independent T-test, and non-normally distributed continuous variables were analyzed with the Mann-Whitney U test. The Chi-square test was used for categorical variables. The statistical significance value was determined as P ≤0.05.

Ethical Permit of the Study: Ethical approval was received from Necmettin Erbakan University, Medical Faculty, Ethics Committee (06.11.2022, Number: 2020/2889) before the study started. All participants provided electronic informed consent.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

A total of 40 women, including 30 patients who were admitted to the Necmettin Erbakan University Meram Medical Faculty Hospital Gynecology and Obstetrics Clinic between January 2019 and January 2020 and diagnosed with recurrent pregnancy loss, and 10 healthy fertile women who applied to the same clinic between the same dates, were included in the study.

Table 1. Comparison of the laboratory findings between the groups.

		RM group (n=30)	Control group (n=10)	P value
NK activity level		2145 (264, 3900)	1380 (500, 4000)	0.662
Patient with high NK activity		17 (56.7%)	5 (50%)	0.714
CD56+CD16+		52.3 (23.7, 70.7)	49.6(23.7, 66.7)	0.574
CD56+CD16+	≥35%	26 (83.3%)	6 (60%)	0.126
CD56+CD16-		47.6(29.2, 76.23)	50.3 (33.2, 76.2)	0.563
CD56+CD16-	≥65%	5(16.7%)	4 (40.0%)	0.126
CD8+		27.4(1.32, 45.52)	24.61(8.66, 36.10)	0.743
CD8+	>35%	4 (13.3%)	1 (10%)	0.783
CD158a+		10.52(2.75, 53.40)	9.48 (2.75, 40.21)	0.662
CD158a+	>8%	17(56.7%)	5 (50.0%)	0.714
CD158-CD8-		53.58 (0.47, 75.58)	57.06(31.68, 75.58)	0.217
CD158-CD8-	>50%	18 (60.0%)	8 (80%)	0.251
CD158+CD8+		6.86 (2.44, 27.79)	5.62(4.05, 8.22)	0.381
CD158+CD8+	>7%	14(46.7%)	3(30.0%)	0.356

NK, natural killer; Data are presented as mean±standard deviation, median (lowest, highest), and number (%); Significant p-values are indicated with "*".

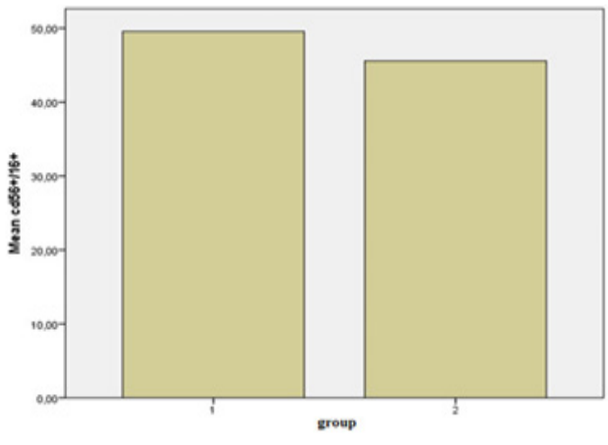

Figure 1. Comparison of CD56+16+ cell percentages in the RM group (1) and the control group (2).

The mean ages of the RM and control groups were not statistically different, 28.2±4.4 and 30.4±2.0, respectively (p=0.462). The mean number of pregnancies was 3 (3, 12) in the RM group and 3 (3, 4) in the control group, with no statistical difference between the two groups (p=0.101).

The median NK activity levels of the groups were not significantly different, with 2145 (264, 3900) in the RM group and 1380 (500, 4000) in the control group (p=0.662). The mean number of cases with high NK activity was 17 (56.7%) in the RM group and 5 (50%) in the control group. There was no statistical difference between the two groups (p=0.714).

The median percentiles of the CD56+CD16+ subgroup were 52.3 (23.7, 70.7) in the RM group and 49.6 (23.7, 66.7) in the control group. There was no statistical difference between the two groups (p=0.574). The median percentiles of the CD56+CD16- subgroup were 47.6 (29.2, 76.23) in the RM group and 50.3 (33.2, 76.2) in the control group. There was no statistical difference between the two groups (p=0.563). (Figure 1)

The median percentiles of the CD8+ subgroup were 27.4 (1.32, 45.52) in the RM group and 24.61 (8.66, 36.10) in the control group. There was no statistical difference between the two groups (p=0.743). The median percentiles of the CD158a+ subgroup were 10.52 (2.75, 53.40) in the RM group and 9.48 (2.75, 40.21) in the control group. There was no statistical difference between the two groups (p=0.662).

The median percentiles of the CD158-CD8- subgroup were 53.58 (0.47, 75.58) in the RM group and 57.06 (31.68, 75.58) in the control group. There was no statistical difference between the two groups (p= 0.217). The median percentiles of the CD158+CD8+ subgroup were 6.86 (2.44, 27.79) in the RM group and 5.62 (4.05, 8.22) in the control group. There was no statistical difference between the two groups (p=0.381).

The laboratory findings of the groups are compared in Table 2.

Discussion

In the last decade, specific properties of NK cells in peripheral blood and uterus have been studied to determine whether Natural Killer cells are associated with miscarriage. Various studies have described increased numbers of uterine and peripheral blood NK cells in women with recurrent miscarriages compared to control fertile women [6, 7]. However, its relationship with miscarriage has not yet been clarified. Patients with recurrent miscarriages may exhibit a lack of inhibition of decidua NK cells, leading to a more active state characterized by higher levels of proinflammatory cytokines. Indeed, dysfunctional cytokine production by Natural Killer cells was documented in peripheral blood, with increased interferon-γ levels and decreased Interleukin-4 [11].

Yasuhiko Ebina et al. investigated the association of NK cell activity with the etiology of recurrent miscarriage in a prospective study and the predictive value of NK cell activity for the outcome of subsequent pregnancies in these women. In that study, peripheral NK cell activity was measured in 160 women with a history of RM and compared according to the etiology of RM and pregnancy outcomes. Patients with idiopathic RM have been found to have significantly higher NK cell activity than those with a known etiology of RM. NK cell activity was higher in women with normal chromosomal karyotype who resulted in

miscarriage and subsequently became pregnant again than in those who gave live birth (p<0.05). Moreover, women with NK cell activity of 33% and above had a higher risk of miscarriage with a normal chromosomal karyotype (relative risk 3.4, 95%, confidence interval 1.3 to 8.7). They concluded that an increase in peripheral NK cell activity was associated with abortions with a normal chromosomal karyotype, which may play a role in the underlying pathophysiology of RM [15]. In another study, Lee et al. reported that high NK cell activity with a cut-off value of 34.3% and above was associated with RM [16].

Chernyshov et al. evaluated the role of increased peripheral NK cell cytotoxicity (NKc) in women with IVF failure. A total of 79 APAS-negative women, including 33 patients with high NKc, were evaluated for the expression of lymphocyte subsets, intracellular cytokines (IFN-γ, IL-4, TNF-α, IL-10), activating markers (CD69, HLA-DR, CD8, KIR(CD158a), CD95 and chemokine receptors (CXCR3, CCR4) using flow cytometry. They reported that NKc levels were higher in women with implantation failure (IF) than in women with successful IVF and that implantation failure was associated with higher CD8, CD158a, and HLA-DR expression in NK cells, activating markers in T-lymphocytes, and levels of IL-4+ T lymphocyte subsets. The predictive value of a single elevated NKc for IVF success was 0.85, while adding the other two abnormal parameters caused it to fall below 0.39. The study identified elevated NKc as a negative, though not critical, factor for implantation in IVF cycles. The immune mechanism of IVF failure includes elevated NKc and several other factors, such as increased CD8 and CD158a expression in NK cells, T lymphocyte activation, and decreased Th2 parameters [17]. However, a systematic review and meta-analysis by Seshadri et al. showed that peripheral NK cell counts were higher in infertile women than in fertile controls. Additionally, in the same study, women with RM had higher numbers and percentages of peripheral NK cells than controls [18].

Despite a body of evidence regarding the relationship between NK cell cytotoxicity and female fertility, different views have been formulated regarding the relationship between the cytotoxic activity of pNK and RM [19]. Although pNK cells contribute to establishing an immune-tolerant environment for placentation, they must have a particular cytotoxic potential to fight infections under normal conditions [20]. Some studies have reported a high rate of pNK cells [21] or cytotoxicity in patients with RM [22]. However, other studies have reported conflicting results showing a lower NK cell ratio or lower pNK cytotoxicity in RM patients compared with fertile controls [23]. A large cohort study suggested that the relationship between subsequent pregnancy outcomes and pNK cytotoxicity is nonlinear and that patients with both low and high pNK cytotoxicity tend to have a high miscarriage rate [24]. Therefore, compared to fertile control, RM patients with both higher pNK cytotoxicity and lower pNK cytotoxicity should be evaluated extensively.

NK cytotoxicity is controlled by the complex interaction between inhibitory and activating receptors. When activating receptor signals are dominant, NK cells exert their cytotoxicity by secreting cytotoxic granules [25].

In the present study, parameters associated with the cytotoxicity of pNK cells were evaluated in women with RM and control fertile women to investigate the etiology of miscarriage in RM patients. Despite the relatively higher median pNK activity level in the recurrent miscarriage group than in the control group, there was no significant difference between the groups in our study (p=0.448). The RM and control groups also did not differ significantly in CD8, CD158a (KIR2DL1) expressions, and IFN-γ amount in pNK cells.

There are many limiting factors in our study. Several factors affecting the level and function of peripheral blood NK cells, namely mental stress age, and race, may affect the results. Some undetected autoimmune diseases or infections may also affect the outcome. Besides, it is unclear whether there is a similarity in cell activity between cycles with conception and without conception. There may be a change in pNK cell number and function when implantation occurs. The activity was measured only once in the present study. Furthermore, subgroups of NK cells may affect pregnancy outcomes.

Conclusion

The present study found no significant difference in the percentages of CD56+dim and CD56+bright pNK cells between the patient group with unexplained RM and the healthy fertile control group. There was also no significant difference in CD8 and CD158a expressions in pNK cells between the patient group with unexplained RM and the healthy fertile control group. Moreover, NK cell activity levels were not significantly different between the two groups.

NK cell function in human reproduction is still poorly understood. All studies collectively indicate changes in the NK cell population in recurrent pregnancy loss and infertility, with results varying depending on whether the material examined is peripheral blood, endometrium, or first-trimester decidua.

It is unclear exactly what kind of relationship, if any, exists between uterine and peripheral blood NK cells. Uterine NK cells play an essential role in early implantation, but whether anomalies cause miscarriages remains to be elucidated. In any case, many studies have shown an independent relationship between peripheral NK cells and RM.

Despite many studies suggesting pNK number or activity as markers of immunological risk in women with RM, its prognostic value remains controversial. Whether changes in NK cell number and activity are the cause or the consequence is not fully understood. Therefore, due to the many arguments in this area, studies with more extensive patient series and control groups are needed to accept or reject the role of NK cell assessment as a predictive test to screen women with infertility or RM.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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